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COMMUNICATION

Copper(I) catalyzed asymmetric 1,2-addition of Grignard reagents to α-methyl substituted α,β-unsaturated ketones†‡

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The first catalytic enantioselective 1,2-addition of Grignard reagents to ketones is presented. This additive-free copper(I) catalyzed 1,2-addition provides chiral allylic tertiary alcohols with an er of up to 98 : 2 and excellent yields due to the complete shift of overwhelming 1,4-selectivity of copper(I)-catalysts towards 1,2-selectivity in the addition reaction to enones.

The catalysed addition of organometallic reagents to aldehydes and ketones is in principle one of the most straightforward methods for the synthesis of chiral enantiopure secondary and tertiary alcohols.[1–3] In spite of their cost, and the transfer of only one of the alkyl groups, the catalytic asymmetric addition of diorganozinc reagents has been particularly well developed and is currently the method of choice.[1–3]

In order to use the inexpensive and readily accessible, but also more reactive, Grignard reagents in these reactions,[4] typically (super)stoichiometric amounts of a chiral additive are required to achieve acceptable enantioselectivities.[4c] First example of the catalytic enantioselective addition of Grignard reagents to aldehydes has been demonstrated recently, albeit requiring a large excess of titanium tetraisopropoxide.[5] The catalytic addition to ketones is considerably more challenging due to enolisation and competitive reduction *via* β-H transfer.[2d] Indeed catalytic non-asymmetric addition of Grignard reagents to ketones has become possible only recently using Zn(II) salts as a catalyst.[6] The *asymmetric* version of these reactions is further complicated due to the smaller steric and electronic differences between the two substituents on the carbonyl group.[2d] Catalytic methods for the asymmetric 1,2-addition of Grignard reagents, to date, are not known.

Here we report on the first enantioselective 1,2-addition of highly reactive Grignard reagents to α-methyl substituted α,β-unsaturated ketones, catalyzed by a Cu(I) salt in combination with a chiral ferrocenyl diphosphine ligand,[7] providing access to highly valuable chiral tertiary allylic alcohols.

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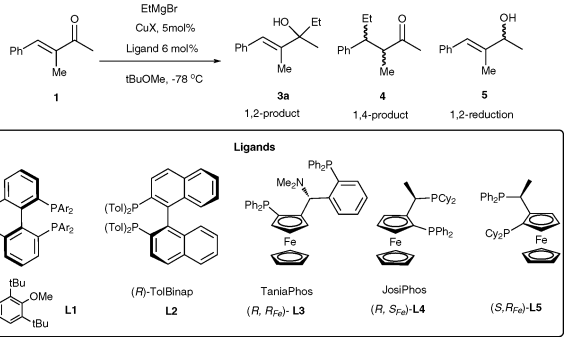
We envisioned that chiral copper(I) based catalysts could be suitable candidates for achieving asymmetric induction in the 1,2-addition of Grignard reagents to ketones. Several examples of copper catalyzed 1,2-additions of organosilanes and organoboranes have been reported by Shibasaki *et al.*[8] Recently it was also reported that copper(I) is capable of catalysing the asymmetric 1,2-reduction of α-substituted enones, thereby providing access to chiral secondary allylic alcohols.[9] Interestingly, copper(I) based catalysts have never been reported for application in the 1,2-addition of highly reactive organometallic reagents to ketones. The main reason is perhaps, that after the pioneering work of Gilman and Straley in 1936[10a] and the discovery of the inherent reactivity of organocopper compounds towards 1,4-addition, copper(I) based reagents and catalysts have been used as the synthetic tool *par excellence* to obtain 1,4-selectivity in addition reactions of Zn-, Al-, Mg- and Li-based organometallic reagents.[10]

An initial screening of reaction conditions indicated that in the presence of 5 mol% of a copper(I) salt, without a chiral ligand present, the reaction proceeded with complete lack of chemoselectivity providing a mixture of products including as expected the 1,2-addition product **3** (Table 1, entry 1). Intriguingly, ligand **L1–L4** significantly increased the chemoselectivity and reactivity of the system toward the 1,2-addition product, albeit with very poor stereoselectivity (entries 2–5). Remarkably, ferrocenyl based diphosphine ligand **L5** turned out to be superior both in terms of 1,2-selectivity and stereoinduction (entry 6). The catalyst precursor CuBr·SMe_2 was compared to other commonly applied Cu(I) salts (entries 6, 7–10) but turned out to be superior. Whilst CuCl, CuI, and Cu-thiophene-2-carboxylate provided the 1,2-addition product with some enantioselectivity, $Cu(OAc)_2$ provided a racemic mixture.

The influence of the solvent on the selectivity of the 1,2-addition was studied with the CuBr·SMe_2/**L5** catalyst. This revealed that ethereal solvents performed better both in terms of regio- and stereoselectivity of the reaction. Whereas Et_2O furnished the 1,2-addition product with good chemoselectivity, the sterically more bulky ethers *t*BuOMe and $(i\text{Pr})_2O$ provided the best regio- and enantioselectivities (entries 6, 11 and 12). Other solvents such as THF and DCM led to almost racemic products (entries 13 and 14). *t*BuOMe was the solvent of choice for further studies. Importantly, with branched-chain Grignard reagents such as *i*BuMgBr a dramatic improvement

Table 1 Optimization of the 1,2-addition of Grignard reagents to ketone **1**



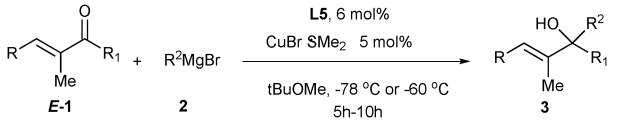
Entry	CuX	L	Solvent	**3a** : **4** : **5**[a] (%)	**3a**, er (%)
1[b]	$CuBr{\cdot}SMe_2$		*t*BuOMe	25 : 21 : 9 : 45	—
2	$CuBr{\cdot}SMe_2$	**L1**	*t*BuOMe	82 : 15 : 3	50 : 50
3	$CuBr{\cdot}SMe_2$	**L2**	*t*BuOMe	84 : 13 : 3	50 : 50
4	$CuBr{\cdot}SMe_2$	**L3**	*t*BuOMe	89 : 7 : 4	52 : 48
5	$CuBr{\cdot}SMe_2$	**L4**	*t*BuOMe	95 : 2 : 3	52 : 48
6	$CuBr{\cdot}SMe_2$	**L5**	*t*BuOMe	97 : 2 : 1	70 : 30
7	CuCl	**L5**	*t*BuOMe	96 : 2 : 2	64 : 36
8	CuI	**L5**	*t*BuOMe	94 : 2 : 4	63 : 37
9[c]	CuTC	**L5**	*t*BuOMe	92 : 3 : 5	59 : 41
10	$Cu(OAc)_2$	**L5**	*t*BuOMe	80 : 6 : 14	51 : 49
11	$CuBr{\cdot}SMe_2$	**L5**	Et_2O	95 : 3 : 2	59 : 41
12	$CuBr{\cdot}SMe_2$	**L5**	$(iPr)_2O$	95 : 3 : 2	69 : 31
13	$CuBr{\cdot}SMe_2$	**L5**	THF	90 : 3 : 7	51 : 49
14	$CuBr{\cdot}SMe_2$	**L5**	DCM	40 : 1 : 59	53 : 47
15[d]	$CuBr{\cdot}SMe_2$	**L5**	*t*BuOMe	96 : 2 : 2	91 : 9
16[e]	$CuBr{\cdot}SMe_2$	**L5**	*t*BuOMe	97 : 1 : 2	92 : 8

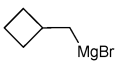
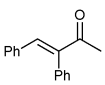
[a] Ratio of **3a** : **4** : **5** was determined by GC analysis. [b] '45' refers to unreacted substrate **1**. [c] CuTC refers to Cu-thiophene-2-carboxylate. [d] *i*BuMgBr was used instead of EtMgBr. [e] Grignard reagent was added to the reaction mixture over 3 h.

of the enantioselectivity to an er of 91 : 9 was observed (entries 6 and 15). A small gain in chemo- and enantioselectivity was obtained by switching from direct to slow addition of the Grignard reagent (entry 16). With optimized conditions in hand the scope of this new reaction was explored.

The scope of the reaction was studied on a variety of α-methyl substituted enones **1** using different Grignard reagents (Table 2). High 1,2-chemoselectivity and yield were obtained for all the substrate and Grignard reagent combinations. Use of the less reactive MeMgBr resulted in complete recovery of the starting material, while addition of PhMgBr led to a racemic 1,2-addition product. Importantly, increasing the sterics in R^1 of the substrate and increasing the sterics of the Grignard reagent provided higher enantioselectivity. Remarkably, we were able to introduce β-branched Grignard reagents with high stereoinduction and yields. *i*BuMgBr afforded the 1,2-addition product in high yield and an er of 92 : 8 (entry 6). Similarly, Grignard reagents bearing a carbocycle afforded the 1,2-addition product in high yield and enantioselectivity (entries 5 and 9). The addition of (2-ethylbutyl)magnesium bromide led to the corresponding product with an er of 96 : 4 and 95% yield (entry 7). Racemic (2-ethyl)hexylmagnesium bromide proved equally effective, with no negative effect on the newly formed stereocenter (entry 8). The results we have obtained with branched-chain Grignard reagents contrast with those known

Table 2 Scope of the $CuBr{\cdot}SMe_2$/**L5** catalyzed 1,2-addition of Grignard reagents to α-methyl substituted α,β-unsaturated ketones **1**

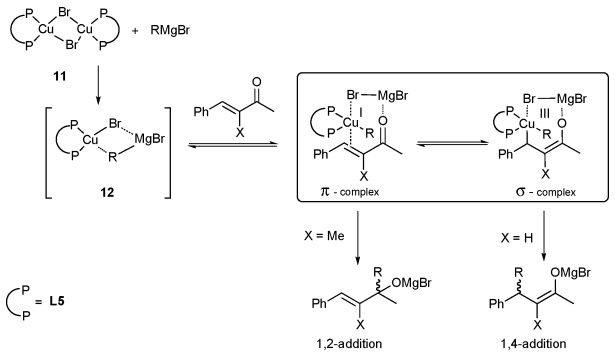


Entry[a]	R, R^1, **1**	R^2MgBr, **2**	**3**	er (yield)[b,c] (%)
1	Ph, Me		**3a**	70 : 30 (95)
2	Ph, *i*Pr		**3c**	83 : 17 (95)
3[d]	Ph, Ph		**3d**	81 : 19 (83)
4	Ph, Ph		**3e**	92 : 8 (94)
5[d]	Ph, Ph		**3f**	88 : 12 (87)
6	Ph, Me		**3b**	92 : 8 (96)
7	Ph, Me		**3g**	96 : 4 (95)
8	Ph, Me		**3h**	96 : 4 (96)
9	Ph, Me		**3i**	94 : 6 (95)
10	Ph, *i*Bu		**3j**	98 : 2 (92)
11			**3k**	84 : 16 (81)
12[d]	Me, Me		**3l**	74 : 26 (85)
13[d]			**3m**	71 : 29 (82)

[a] Conditions: addition of 1.3 equiv. R^2MgBr to a 0.15 M solution of **1** in *t*BuOMe at −78 °C. [b] Yield of the isolated product **3**. [c] The er of **3** was determined by chiral HPLC analysis (see ESI). [d] The reaction was performed at −60 °C.

for the 1,2-addition methodologies to ketones based on diorgano Zn/Ti[2,3] systems which are restricted to the use of linear alkyl groups and aryl moieties. Replacing a methyl with a phenyl substituent at the α-position of the enone led to a slight decrease in selectivity (Table 2, compare entries 6 and 11). Due to their lower inherent reactivity, the aliphatic enones were recovered unchanged at −78 °C. Increasing the reaction temperature to −60 °C furnished the 1,2-addition product with both cyclic and acyclic aliphatic eneones in high yields albeit with lower enantioselectivity (entries 12 and 13).

The presence of Cu in the catalytic system is essential for all the reactions discussed so far; no tertiary alcohols are formed



Scheme 1 Tentative mechanistic pathway for the 1,2-addition of Grignard reagents to α,β-unsaturated ketones catalyzed by $CuBr{\cdot}SMe_2$/**L5**.

when using only **L5**. Furthermore, our experimental results show that the presence of an α-substituent and an adjacent unsaturation in the substrate are important to obtain the desired 1,2-addition products with high regio- and enantioselectivity. The use of aliphatic ketones led to the 1,2-addition products in low yields and no enantiodiscrimination. The importance of Cu, an adjacent unsaturation and the formation of 1–2% of 1,4-addition product shows a mechanistic similarity to the well-studied Cu(I) catalyzed 1,4-addition of organometallics.[11] Equipped with the experimental findings presented here, the working hypothesis is that our system initially follows the trends observed in 1,4-addition which consists of formation of copper/ligand complex **11**, its transmetallation by the Grignard reagent (complex **12**), reversible formation of a copper–olefin π-complex followed by formal oxidative addition to the β-carbon leading to a Cu(III) intermediate (σ-complex) (Scheme 1).[11] Most probably, the presence of an α-substituent prevents the formation/accumulation of Cu(III) species, which in turn prevents 1,4-addition and favors 1,2-addition.

In summary, for the first time we have been able to demonstrate that it is possible to achieve Cu(I) catalyzed asymmetric 1,2-additions to α-substituted enones using inexpensive, highly reactive Grignard reagents and the use of stoichiometric amounts of additives is not required. The discovery of this novel catalytic system gives access to chiral branched tertiary alcohols with excellent yields and an er up to 98 : 2.

Application of this concept to simple aromatic ketones as well as mechanistic studies to address the current limitations of the methodology which are lower enantioselectivities with aliphatic substrates and non-branched Grignard reagents are ongoing and will be reported in due course.

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